INTRODUCTION TO PHARMACODYNAMICS AND MECHANISM OF DRUG ACTION

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AP Pharmacology

Sources:

Bertram G. katzung Basic & Clinical Pharmacology 15th Edition

Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition.

1. A 16 years old girl suffering from seasonal rhinitis started a therapy with loratidine an anti-histamine. Which of the following term best describes the intrinsic ability of a drug to bind with receptors?

   A) Intrinsic activity
   B) Potency
   C) Efficacy
   D) Affinity
   E) Receptor Activities

2. Which of the following onset of action of various signaling mechanisms is correctly matched?

   A) Cytokine receptor- Milliseconds
   B) G- Coupled linked receptor- Days
   C) Insulin receptors- Minutes
   D) Ion channel linked receptor- Hours
   E) Steroid receptors- Seconds

3. Drugs like corticosteroids are capable of targeting intracellular receptors secondary to their ability to

   A) Diffuse through lipid membranes
   B) Dimerise upon ligand binding
   C) Induce conformational change in the receptor
   D) Interact with adenyl cyclase
   E) Undergo phosphorylation

1. Clonidine is an agonist that may produce hypertensive crisis upon sudden withdrawal. this is due to decrease in number of its receptors that mediate a decrease in BP. Such a phenomenon is called

   A) Desensitization
   B) Down regulation
   C) Tolerance
   D) Tachyphylaxis
   E) Up regulation

2. A 60-year-old male patient with chronic hypertension is treated with a beta-blocker medication. Beta-adrenergic receptors, which are GPCRs, play a crucial role in regulating heart rate and blood pressure. The medication blocks the effects of the sympathetic nervous system. Which of the following is the primary signaling pathway activated by the beta-adrenergic receptor, a type of GPCR?

   A) Activation of phospholipase C
   B) Activation of adenylyl cyclase to increase cAMP levels
   C) Opening of ion channels for calcium influx
   D) Activation of protein kinase A (PKA) by DAG

3. A 45-year-old male presents with symptoms of muscle weakness and fatigue. Upon further examination, it is revealed that his condition is associated with a defect in acetylcholine receptors at the neuromuscular junction. This leads to abnormal functioning of ion channels that mediate neurotransmitter release. Which of the following types of ion channels is primarily involved in this transduction mechanism?
   A) Voltage-gated potassium channels
   B) Ligand-gated sodium channels
   C) Voltage-gated calcium channels
   D) Ligand-gated chloride channels
   E) Voltage-gated chloride channels

1. A 22-year-old student presents with anxiety-like symptoms and difficulty concentrating. Upon neurological testing, it is found that there is an alteration in the synaptic transmission in the brain, which might involve a specific type of ion channel linked to GABAergic signaling. Which of the following ion channels is most likely involved in this transduction mechanism?

   A)NMDA receptors (ligand-gated calcium channels)
   B) GABA-A receptors (ligand-gated chloride channels)
   C) AMPA receptors (ligand-gated sodium channels)
   D) Voltage-gated sodium channels
   E) TRP (Transient Receptor Potential) channels

2. A 60-year-old patient with lung cancer is found to have a mutation in the epidermal growth factor receptor (EGFR). This mutation leads to uncontrolled cell growth and proliferation. Which of the following is most likely to be involved in the mechanism of tumorigenesis in this case?

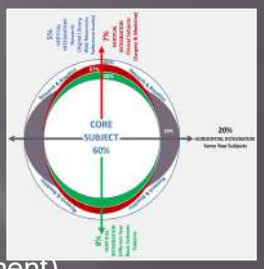
   A) Inhibition of MAP kinase pathway
   B) Activation of tyrosine kinase signaling pathways
   C) Decrease in cytokine production
   D) Inhibition of receptor internalization
   E) Increased G-protein activity

LEARNING OBJECTIVES

- At the end of session, student should be able to
  - Discuss different ways of drug interaction
  - Define receptors, its types and distribution
  - Define ligand
  - Discuss different receptor ligand interaction
  - Describe different receptor signal transduction mechanism

SEQUENCE OF LECTURE

- Core Subject
- Spiral Integration
- Horizontal Integration
- Vertical integration
- Digital Library References (Research & Bioethics)
- EOLA(End of lecture assessment)



PHARMACODYNAMICS

- DEFINITION

  "Study of biochemical and physiological effects of drugs and their mechanisms of action."
- INCLUDES
  - **Mechanism of action**
  - **Effects**
  - **Adverse effects**
  - **Contraindications**
  - **Drug interactions**

Core subject

- DRUG ACTION

  It is the initial combination of the drug with its receptor resulting in a conformational change in the latter.
- DRUG EFFECT

  It is the ultimate change in biological function brought as a consequence of drug action,through a series of intermediate steps(tansduction).

Core subject

- Drug undergo 3 phases to reach site of action
  - Pharmaceutical- dissociation, disintegeration
  - Pharmacodynamic
  - Pharmacokinetic

Core Subject

TYPES OF DRUG ACTION

- NON-RECEPTOR MEDIATED (Physiochemical, non cellular)
- RECEPTOR MEDIATED, (Pharmacodynamic, cellular)

Core subject

NON RECEPTOR DRUG INTERACTIONS

- Physical Mechanisms
- Chemical Mechanisms

Core subject

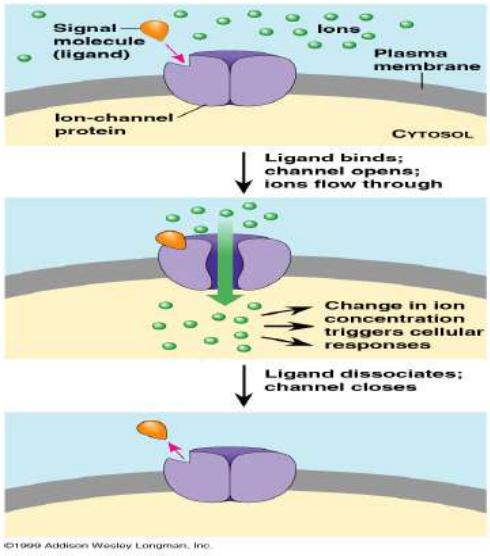
Signal molecule binds as a ligand at a specific site on the receptor

↓

Conformational changes open the channel allowing ions to flow into the cell

↓

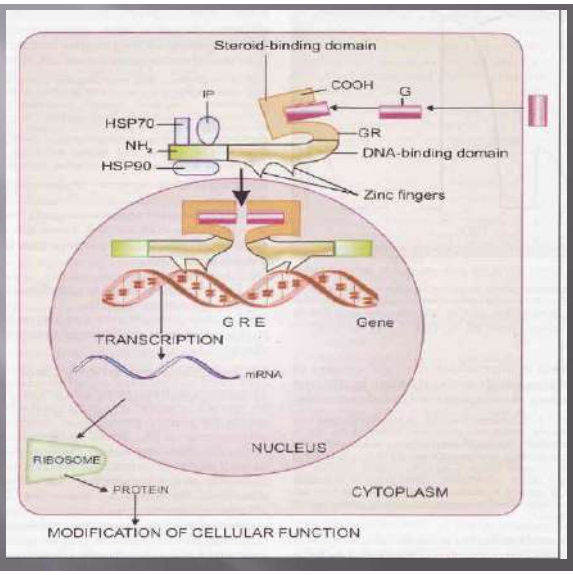
The change in ion concentration within the cell triggers cellular responses



INTRACELLULAR RECEPTORS

- A lipid soluble ligand crosses the membrane and acts on a intracellular receptor.
- Some receptors are located in the cytoplasm and some are located in the nucleus.
- delayed response-within minutes to several hours.
- Examples include

  Corticosteroids,mineralocorticoid,sex steroids,vitamin A and D,thyroxine.

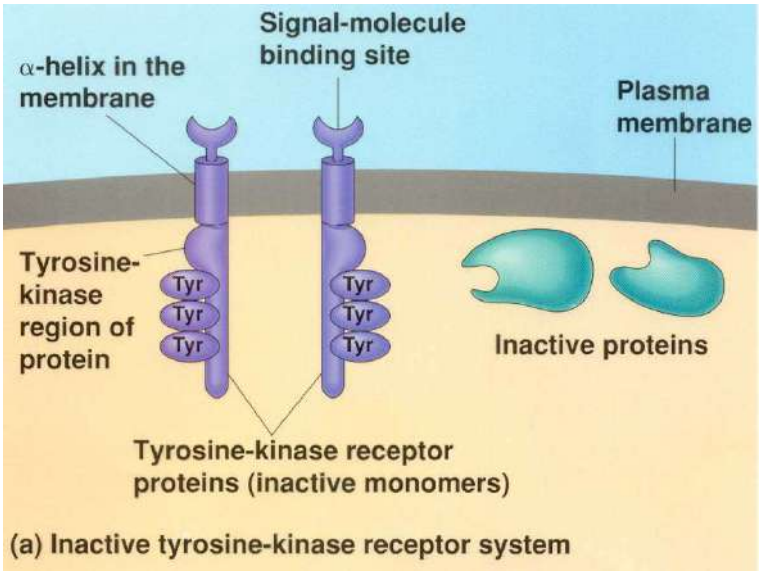


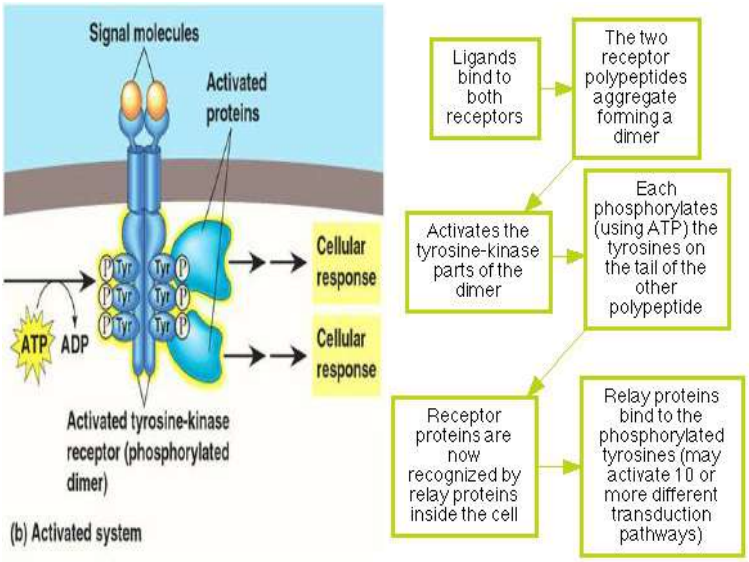
The glucocorticoid (G) penetrates the cell membrane and binds to the glucocorticoid receptor (GR) protein that normally resides in the cytoplasm in association with 3 other proteins, viz. heat shock protein 90 (HSP90), HSP70 and immunophilin (IP). The GR has a steroid binding domain near the carboxy terminus and a mid region DNA binding domain having two 'zinc fingers', each made up of a loop of amino acids with chelated zinc ion. Binding of the steroid to GR dissociates the complexed proteins (HSP90, etc) removing their inhibitory influence on it. A dimerization region that overlaps the steroid binding domain is exposed, promoting dimerization of the occupied receptor. The steroid bound receptor dimer translocates to the nucleus and interacts with specific DNA sequences called 'glucocorticoid responsive elements' (GREs) within the regulatory region of appropriate genes. The expression of these genes is consequently altered resulting in promotion (or suppression) of their transcription. The specific mRNA thus produced is directed to the ribosome where the message is translated into a specific pattern of protein synthesis, which inturn modifies cell function.

LIGAND REGULATED TRANSMEMBREANE ENZYMES

- Receptor has two domains-intracellular and extracellular domain.
- Ligand bind to the extracellular domain which in turn is bound to the intracellular domain through a single transmembrane stretch of peptide chain.
- Intracellular domain has enzymatic activity may be
  - Tyrosine kinase
  - Serine kinase
  - Guanylyl cylase

- Ligand bind to the extracellular domain of receptor and undergo dimerization.
- Cascade of phosporylation and dephosphorylation occur.
- Signaling occur within minutes and hours.
- Examples include
  - Insulin,EGF,ANP,TGFβ





Transmembrane enzyme-linked receptors

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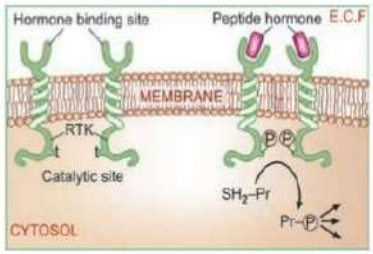
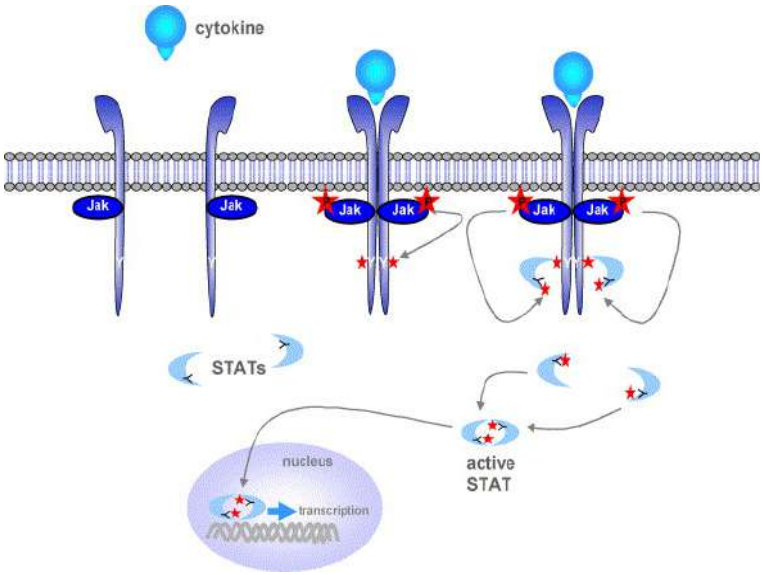


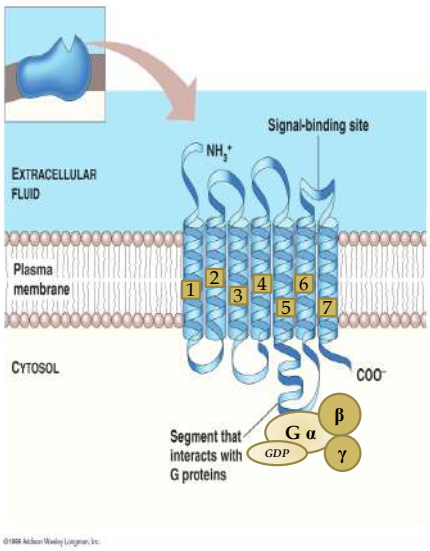
Model of receptor tyrosine kinase, an enzyme-linked receptor

CYTOKINE RECEPTORS

- Similar to transmembrane except that the intracellular domain does not have enzymatic activity.
- Dimerization causes activation of JAK proteins.
- This causes phosphorylation of STAT proteins.
- Dimerization of STAT protein results in their separation from the receptors and they enter into the nucleus.
- Transcription of certain proteins.
- E.g.Growth harmone,Interferon,Erythropoietin



RECEPTORS LINKED TO G-PROTEINS



GPCR Structure:

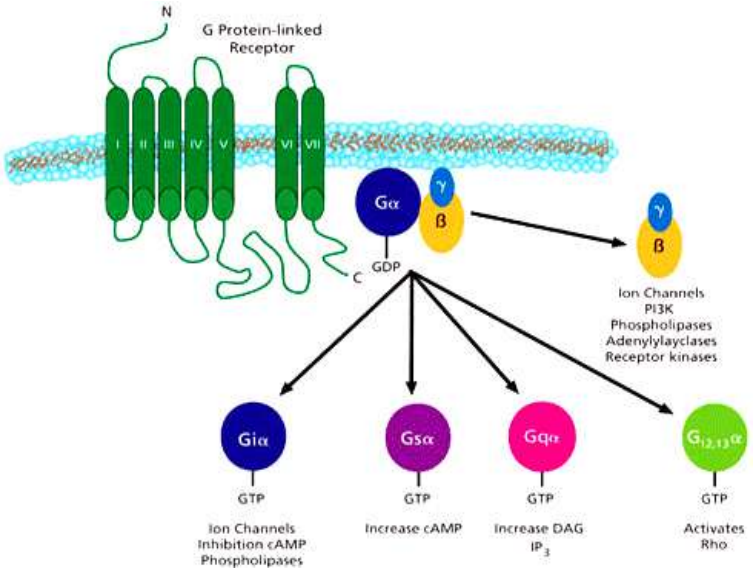
- Single polypeptide chain threaded back and forth resulting in serpentine shaped 7 transmembrane alpha helices with 3 loops extracellularly & 3 loops intracellularly.
- There's a G protein attached to the cytoplasmic side of the membrane.
- Amino terminal lies extracellularly & carboxy terminal on cytosolic side.

G-PROTEIN

- Consist of three subunits: α , β , γ
- α subunit has enzymatic activity and catalyses conversion of GDP to GTP.
- After binding of ligand,G- proteins are stimulated which further associate with various enzymes and ion channels, causing activation and inactivation as the case may be.
- Signaling occur within seconds to minutes.
- E.gs.Serotonin,Adrenergic amines,Muscaranic acetylcholine,Peptide hormones.

CLASSES OF G- PROTEINS

- 3 major classes
  - Gs
  - Gi
  - Gq
- Gs stimulate adenyl cylase(ATP into cAMP)
- Gi inhibits adenyl cylase
- Gq stimulates phospholipase C(converts PIP2 into IP3 and DAG)



cAMP AS A SECOND MESSANGER

- cAMP stimulate cAMP dependant protein kinases.
- cAMP regulates many aspects of cell function like
  - ❖Different enzymes-increased glycogenolysis
  - ❖Ion channels-increased activity of voltage gated calcium channels in cardiac muscles causing increased calcium influx and hence increased heart rate and force of contraction.

- In smooth muscles,cAMP phosphorylates the enzyme myosin light chain kinase , thus myosin light chains are dephosphorylated and his accounts for the smooth muscle relaxation.

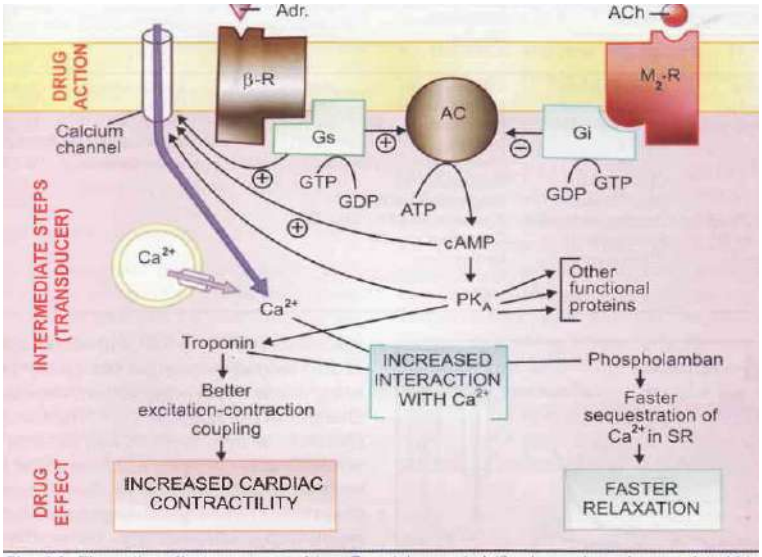


Fig. 4.6: The action-effect sequence of two G-protein coupled (β adrenergic and muscarinic M_2)

Adrenaline (Adr) binds to β-adrenergic receptor (β-R) on the cell surface inducing a conformational change which permits interaction of the G-protein binding site with the stimulatory G-protein (Gs). The activated Gs now binds GTP (in place of GDP), causing its active subunit to dissociate and inturn activate the enzyme adenylyl cyclase (AC) located on the cytosolic side of the membrane. ATP is hydrolysed to cAMP which phosphorylates and thus activates cAMP dependent protein kinase (PK_A). The PK_A phosphorylates many functional proteins including troponin and phospholamban, so that they interact with Ca^{2+}, respectively resulting in increased force of contraction and faster relaxation. Calcium is made available by entry from outside (direct activation of myocardial membrane Ca^{2+} channels by Gs and through their phosphorylation by PK_A) as well as from intracellular stores.

One of the other proteins phosphorylated by cAMP is phosphorylase kinase which then activates the enzyme phosphorylase resulting in breakdown of glycogen to be utilized as energy source for increased contractility.

Action of acetylcholine (ACh) on muscarinic M_2 receptor (M_2-R), also located in the myocardial membrane, can similarly activate an inhibitory G-protein (Gi) which then opposes the activation of AC by Gs.

DAG AND IP3 AS SECOND MESSENGERS

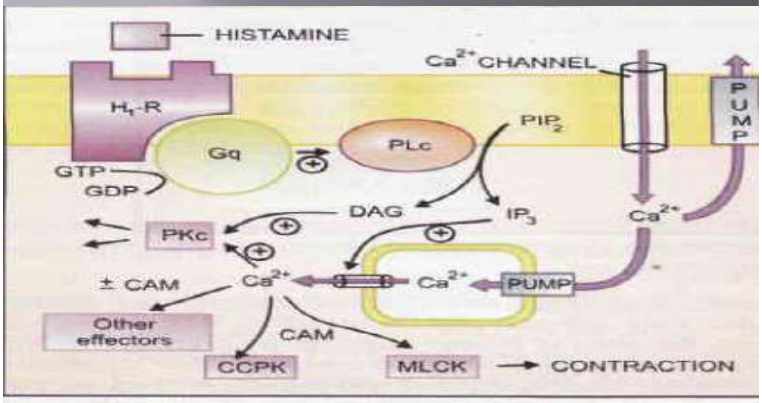
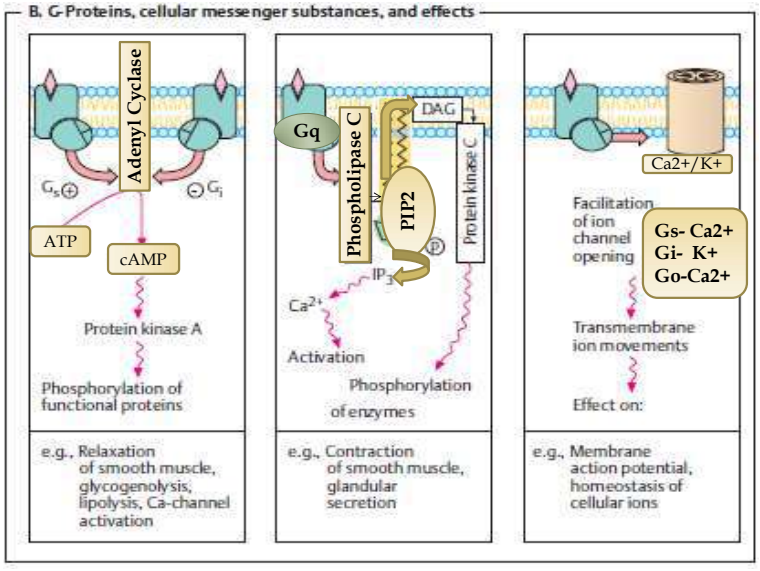


Fig. 4.7: The important steps of phospholipase C(PLc pathway of response effectuation (in smooth muscle)

The agonist, e.g. histamine binds to its H_1 receptor (H_1 R) and activates the G-protein G_q, which inturn activates membrane bound phospholipase C (PLc) that hydrolyses phosphatidyl inositol 4, 5-bisphosphate (PIP_2), a membrane bound phospholipid. The products inositol 1, 4, 5-trisphosphate (IP_3) and diacylglycerol (DAG) act as second messengers. The primary action of IP_3 is facilitation of Ca^{2+} mobilization from intracellular organellar pools, while DAG in conjunction with Ca^{2+} activates protein kinase C (PKc) which phosphorylates and alters the activity of a number of functional and structural proteins. Cytosolic Ca^{2+} is a veritable messenger: combines with calmodulin (CAM) to activate myosin light chain kinase (MLCK) inducing contraction, and another important regulator calcium-calmodulin protein kinase (CCPK). Several other effectors are regulated by Ca^{2+} in a CAM dependent or independent manner

cGMP AS A SECOND MESSENGER

- Less common than cAMP
- Causes relaxation of vascular smooth muscle by kinase mediated mechanism that results in dephosphorylation of myosin light chains.
- Examples include
  - ANP
  - NO



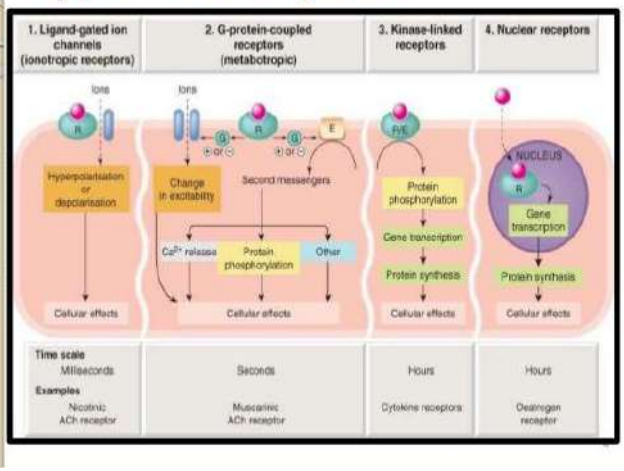
EXAMPLES OF RECEPTORS THAT ARE COUPLED BY G-PROTEINS

Receptor Types	Coupling Protein	Effector	Effector Substrate	Second Messenger Response	Result
M_1, M_3, α	G_q	Phospholipase C	Membrane lipids	↑ IP_3 ↑ DAG	↑ Ca^{2+} ↑ Protein kinase
β, D_1	G_s	Adenylyl cyclase	ATP	↑ cAMP	↑ Ca^{2+} influx ↑ Enzyme activity
α_2, M_2	G_i	Adenylyl cyclase	ATP	↓ cAMP	↓ in Ca^{2+} influx and enzyme activity

INACTIVATION OF SECOND MESSENGERS

- cAMP and cGMP
- DAG
- IP3
- Ca++

Types of receptors



HORIZONTAL/VERTICAL INTEGERATION

- Emergence of diseases due to distruption of signal transduction pathways

BIOETHICS

- Loss of selectivity of receptors at high doses

RESEARCH

- Wu L, Cheng Y, Geng D, Fan Z, Lin B, Zhu Q, Li J, Qin W, Yi W. O-GlcNAcylation regulates epidermal growth factor receptor intracellular trafficking and signaling. Proceedings of the National Academy of Sciences. 2022 Mar 8;119(10):e2107453119.
- Muromoto R, Oritani K, Matsuda T. Current understanding of the role of tyrosine kinase 2 signaling in immune responses. World Journal of Biological Chemistry. 2022 Jan 1;13(1):1.

END OF LECTURE ASSESMENT (EOLA)

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